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EDITORIAL

10 myths about frusemide

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Background

Frusemide is the most frequently used diuretic in critically ill patients [1]. It exerts its action by selectively blocking the $Na^+/K^+/2Cl^-$ co-transporter in the luminal membrane of the thick ascending limb of the loop of Henle (Supplementary Fig. S1). To reach the site of action, it is first taken up by the proximal cells via organic anion transporters and then secreted into the luminal space from where it is transported to the distal tubule. Frusemide generates greater loss of water than sodium loss, resulting in the production of hypotonic urine. Diuretic resistance is not uncommon in patients receiving prolonged therapy with loop diuretics. Furthermore, concern has been raised that diuretic use may be associated with harmful effects, including acute kidney injury (AKI). This has led to uncertainty among clinicians about when and how to use frusemide safely and effectively in critically ill patients with and without AKI [1]. Here, we address ten common myths about frusemide and its application in critically ill patients (Fig. 1).

Myth #1 Frusemide causes AKI.

No, it does not.

Frusemide promotes diuresis and is particularly useful in patients with fluid overload. However, it is a common conception that diuretics may cause AKI. In fact, few studies have identified diuretic use as a risk factor for AKI [2]. However, most reports did not distinguish between different aetiologies of AKI and included patients with AKI due to hypovolaemia. It is very likely that inappropriate use of diuretics in this patient population contributes to the development of AKI. However, when used appropriately in patients with fluid overload, frusemide may actually resolve AKI, presumably due to resolution of intrarenal congestion and reduction of renal oxygen consumption [3, 4].

Myth #2 Frusemide and fluids together can prevent AKI in high-risk patients.

Probably not.

There is a common belief that the co-administration of frusemide and fluids increases diuresis without causing hypovolaemia. In fact, automated matched hydration systems using diuretics and fluids together exist for the prevention of contrast-associated AKI (CA-AKI). While some authors found a reduction in the incidence of CA-AKI [5], studies in patients with AKI did not demonstrate a beneficial effect on progression of AKI [6]. In general, fluids should be considered as therapy for patients with intravascular hypovolaemia and diuretics should be reserved for patients with intravascular hypervolaemia.

Myth #3 Frusemide is contraindicated in AKI.

No, it is not.

Frusemide is indicated in patients with fluid overload, including those with AKI. However, higher doses may be needed in AKI, especially in severe AKI where the risk of diuretic resistance is higher, too. Frusemide also has a role in the management of hyperkalaemia [3]. Finally, frusemide can be used as a diagnostic tool in AKI when assessing tubular function and risk of progression to higher stages of AKI (i.e. frusemide stress test) [7].

Myth #4 Frusemide can kick-start kidney function.

No, this is not the case.

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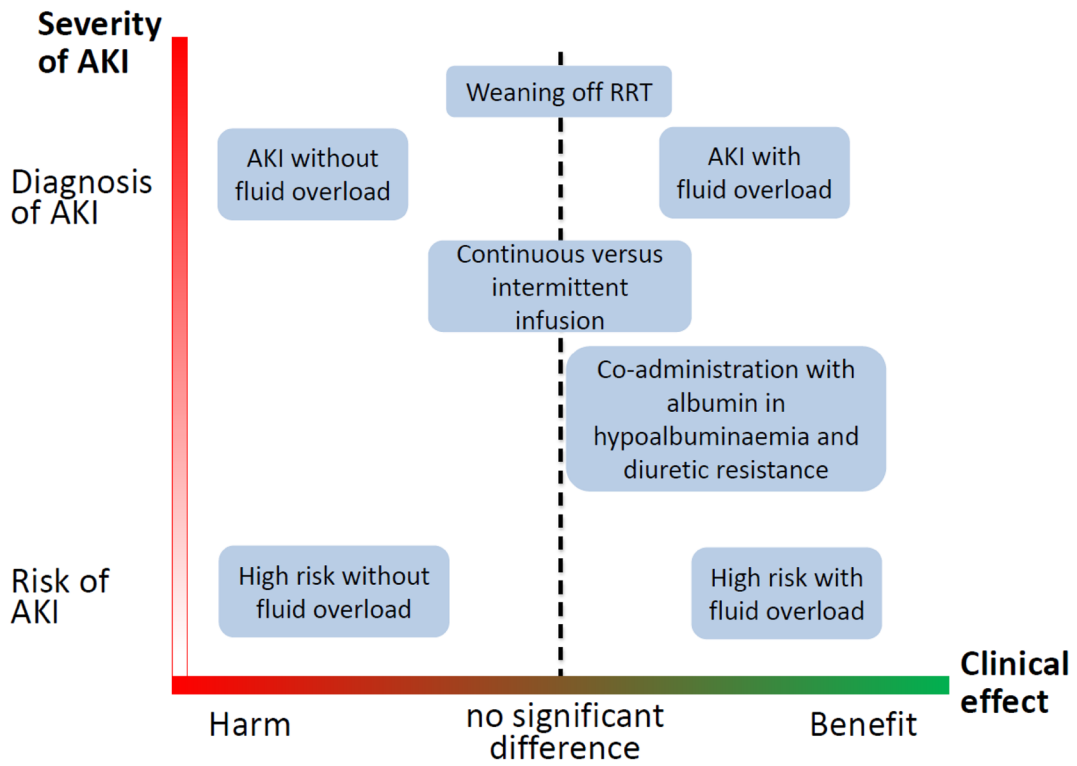

Fig. 1 Clinical effects of frusemide therapy

Frusemide may lead to significant diuresis in patients with AKI. However, this has to be regarded as an indication of functioning tubular cells, rather than a direct beneficial effect of frusemide on renal function [3]. Repeated doses of frusemide, especially in high doses and in anuric patients, may lead to a significant increase in side effects, in particular ototoxicity [3]. In patients with fluid overload, who are not diuretic-responsive, there is no role for repeated frusemide application [4]. In this situation, extracorporeal fluid removal should be considered.

Myth #5 Frusemide works better if given together with albumin.

It depends.

In plasma, frusemide is highly protein-bound, and severe hypoalbuminaemia is associated with impaired frusemide secretion into the tubular lumen. The evidence supporting the combined use of albumin and frusemide is sparse. In a study including patients with liver cirrhosis and ascites, the administration of premixed loop diuretic and albumin (40 mg frusemide and 25 g albumin) did not enhance the natriuretic response [8]. In contrast, a randomized controlled cross-over study in 24 patients with chronic kidney disease (CKD) and hypoalbuminaemia showed a significant increase in urine volume with frusemide and albumin [9]. However, at 24 h, there were no longer any significant differences. A meta-analysis including 10 studies demonstrated better control of fluid balance with co-administration of frusemide and albumin in hypoalbuminaemic patients [10]. Studies in patients with normal blood protein levels are inconclusive, pointing to no direct benefit of combined infusion in these patients.

Myth #6 Frusemide infusion is more effective than frusemide boluses.

No, it is not.

Several randomized controlled trials (RCTs) and meta-analyses showed that sustained diuresis is easier to achieve with continuous frusemide infusion compared to intermittent bolus therapy [11], but there is no evidence of better outcomes, including mortality, length of hospital stay, effect on renal function or electrolyte disturbances.

Myth #7 Frusemide can prevent renal replacement therapy (RRT).

No, it can't.

Frusemide has a role in inducing diuresis in patients with fluid overload. If diuretic responsive, the administration of frusemide may buy time before RRT can be initiated. A meta-analysis reported that the administration of loop diuretics was associated with shorter duration of RRT [12]. However, frusemide has no direct effect on chances of renal recovery. A pilot trial (the SPARK study) compared low-dose frusemide versus placebo in patients with early AKI and found no difference in the rate of worsening AKI or need for RRT [6].

Myth #8 Frusemide helps to wean anuric patients from RRT.

No, it does not.

In patients treated with RRT, increasing diuresis is a common reason for discontinuing RRT, and diuretics are frequently used for this purpose. However, there is no evidence that diuretics are effective at improving creatinine clearance or inducing renal recovery [12, 13]. However, it should be noted that frusemide was also associated with a higher incidence of ototoxicity, a risk that may be particularly relevant to anuric patients at increased risk of frusemide accumulation [12].

Myth #9 Frusemide-induced diuresis after AKI implies full renal recovery.

No, it does not.

While frusemide administration may lead to increased urine output (UO) in patients with AKI [12], frusemide-induced diuresis after AKI must not be considered a sign of *full* and permanent renal recovery. Even patients who experienced only a single episode of AKI and recovered excretory function remain at increased risk of CKD and increased mortality.

Myth #10 Frusemide should be stopped if serum creatinine is increasing, indicating worsening renal function.

No, not necessarily.

Many patients with acute heart failure have a rise in serum creatinine of 0.3 mg/dl or more during diuretic therapy [14]. However, this must not automatically be interpreted as a sign of *true* worsening renal function (WRF) associated with impaired outcome. Since creatinine is measured as a concentration in serum, an isolated increase in serum creatinine in combination with a rise in haematocrit may simply be a sign of reduction in intravascular volume and effective decongestion. Importantly, it may also be associated with better outcomes. This phenomenon is termed *pseudo* WRF [14]. A similar effect was observed in the FACTT trial, where restricted fluid therapy using substantial diuretic dose improved weaning from respirator but was associated with increased serum creatinine by nearly 0.3 mg/dl. Despite that, the requirement of RRT was even lower in this group [15].

Electronic supplementary material
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